IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Patent Application of:
Gunther Bellmann et al.
Serial No.: 10/665,937
Filed: September 18, 2003
For: Dexamethasone Gel

Docket No.: P02428-C1
Examiner: Zohreh Fay
Art Unit: 1618

CERTIFICATE OF MAILING

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Judith Davis

Judith Davis

APPEAL BRIEF

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

By Notice of Appeal filed on April 25, 2006, Applicant appeals the Final Rejection in the above-identified application dated February 1, 2006, and submits this Brief in support thereof. Authorization to charge the fee under 37 CFR 41.20(b)(2) to Deposit Account No. 02-1425 is provided in the transmittal letter accompanying this Appeal Brief. Additionally, a Petition for a Three-Month Extension of Time is being filed concurrently with this Appeal Brief.

I. Real Party in Interest

The real party in interest in this appeal is Bausch & Lomb Incorporated and its subsidiary Dr. Gerhard Mann Chem.-Pharm. Fabrik GMGH, as evidenced by the Assignment recorded at Reel 011030, Frame 0891 in parent application Serial No. 09/486,460.

II. Related Appeals and Interferences

Applicant is not aware of any other appeals or interferences which will directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

III. Status of Claims

Claims 7-16 are currently pending.

Claims 7-16 stand rejected.

Claims 7-16 form the basis of this appeal.

IV. Status of Amendments

No amendments have been filed following the Final Rejection of February 1, 2006.

V. Summary of Claimed Subject Matter

Independent claim 7, the sole independent claim, defines an ophthalmic gel preparation comprising: dexamethasone dihydrogenphosphate disodium; a gel forming, pharmaceutically acceptable substance in an amount effective for adjusting the viscosity of the preparation so that the preparation has the form of a gel; and a pH regulating component in an

amount effective to provide the preparation with a pH value above 7.3. Dependent claim 8 defines a more preferred pH value range of between 7.6 and 8.2.

The presently claimed invention recognized that ophthalmic gel preparations comprising dexamethasone dihydrogenphosphate disodium not only should be effective and non-irritating to eye tissue, but also should have sufficiently long shelf-life stability so that the formulations do not lose their effectiveness while stored. Specifically, it was found that the addition of a gelling agent, such as a carbomer, to an ophthalmic gel preparation comprising dexamethasone dihydrogenphosphate disodium, at near neutral pH (pH 7 to about 7.3), resulted in considerable decomposition of the dexamethasone active. According to the present invention it was surprisingly found that an increase of the pH value above 7.3 may avoid the foregoing decomposition problems. Accordingly, the presently claimed invention refers to an ophthalmic gel preparation with a pH value above 7.3. See, for example, specification page 3.

VI. Grounds of Rejection to be Reviewed on Appeal

The sole ground of rejection raised by this appeal is:

Whether claims 7-16 were improperly rejected as unpatentable under 35 USC § 103(a) over Mazuel et al. (US 4,861,760), Rozier (US 5,304,559) and GB '091 (GB 2007091).

VII. Argument

Claims 7-16 were improperly rejected as unpatentable under 35 USC § 103(a) over Mazuel et al. (US 4,861,760), Rozier (US 5,304,559) and GB '091 (GB 2007091).

A. The Cited References

Mazuel et al. discloses pharmaceutical compositions intended to be administered as a non-gelled liquid form and intended to gel in situ. The compositions contain a certain polysaccharide in aqueous solution, the polysaccharide being the type which undergoes liquid-gel phase transition so as to gel in situ under the effect of an increase in ionic strength of the physiological fluid (e.g., lacrimal fluid). See, for example, the Abstract.

Rozier discloses pharmaceutical compositions containing at least one 4-quinolone derivative. Rozier is concerned with preventing crystal growth of these compounds in suspension. There is no mention of storage stable dexamethasone-containing formulations, nor is there any indication that a pH value above 7.3 may be used to increase the stability of a pharmaceutical preparation. In contrast, Rozier teaches that in order to obtain increased stability, an active compound may be complexed with a certain divalent metal ion. See, for example, the Abstract.

GB '091 discloses ophthalmic compositions in the form of a gel, comprising an aqueous solution of a carboxyvinyl polymer, a water-soluble basic substance, and an ophthalmic drug admixed therewith, the gel having a pH of 5 to 8 and a viscosity of 1,000 to 10,000 centipoise at 20°C. See, for example, the Abstract. Among Examples 1-40, only

Examples 6 and 28 have a pH value above 7.3, and these examples do not include a dexamethasone.

B. Claims 7 and 9-16

First, it is submitted the cited references teach away from the presently claimed invention.

In Example 3 of Mazuel et al., dexamethasone phosphate solutions are disclosed, but the solutions of Mazuel et al. are designed to gel only upon contact with the eye's liquids. At the Abstract and at column 2, lines 16 et seq., Mazuel et al. explicitly states that the invention relates to a pharmaceutical composition that "is intended to be administered as a non-gelled liquid form and is intended to gel in situ" meaning that the Mazuel et al. preparation forms a gel only upon contact with the physiological fluid, namely, human lacrimal fluid. Such statements are repeated throughout the cited reference; see, for example, column 2, lines 30-34:

> "the composition, which takes the form of a liquid before its introduction into the eye, undergoes a liquid-gel phase transition, and hence changes from the liquid phase to the gel phase, once it is introduced into the eye, as a result of the ionic strength of the physiological fluid which is in this case, the lacrimal fluid.

See, also, column 2, lines 56 to 61:

> "Furthermore, in the case of already gelled or semi-gelled solid compositions, it is not possible to administer them by volumetric means, especially when they come from a multi-does container."

Applicant is mindful that the Examiner is entitled to give the claims their broadest reasonable interpretation. However, it is submitted that the present claims do not read on a

formulation that gels upon exposure to eye fluid. First, claim 7 clearly states the preparation has the form of a gel. Second, claim 7 states the preparation has a pH above 7.3 – what would the pH value of the Mazuel et al. formulation be after contacting eye fluid? There is no evidence in Mazuel et al. that such later-formed gels have a pH value above 7.3; in fact, the properties of the later-formed gels are not disclosed at all in this reference. Thus, Mazuel et al. teaches away from the storage-stable gel preparations defined in the rejected claims.

Second, no *prima facie* case of obviousness has been established. It is submitted the rejection relies on selectively choosing various limitations of the present claims from the various cited references, without the requisite motivation.

Mazuel et al., as pointed out above, does not even relate to an ophthalmic preparation having the form of a gel and having the components and pH values defined in the rejected claims. Rozier does not mention storage stable dexamethasone-containing formulations, nor is there any indication that a pH value above 7.3 may be used to increase the stability of a pharmaceutical preparation. In contrast, as pointed out above, Rozier teaches that in order to obtain increased stability, this problem is addressed by complexing the active compound with a certain divalent metal ion. GB '091 discloses, as pointed out above, ophthalmic compositions in the form of a gel, comprising an aqueous solution of a carboxyvinyl polymer, a water-soluble basic substance, and an ophthalmic drug admixed therewith, the gel having a pH of 5 to 8 and a viscosity of 1,000 to 10,000 centipoise at 20°C. Among Examples 1-40, only Examples 6 and 28 have a pH value above 7.3, and these examples do not include a dexamethasone.

In summary, none of the cited references: recognizes any problem with stability of dexamethasone dihydrogenphosphate disodium-containing gel preparations; suggests adjusting pH to any value (let alone the pH value in the present claims) to solve the problem of storage stability for such preparations; nor discloses dexamethasone dihydrogenphosphate disodium-containing gel preparations with the claimed pH range.

At best, GB '091 discloses that gel preparations may have a pH of 5 to 8. However, Applicant submits that since GB '091 recognizes no criticality of pH value, and recognizes no problem with storage stability of the pharmaceutically active component, the GB '091 disclosure actually evidences the non-obviousness of the presently claimed invention.

Stated differently, it is true, as implicitly asserted in past rejections, that various formulations having a pH value within the range recited in the rejected claims were known. However, the cited references do not provide the requisite motivation to select a pH value above 7.3 for the claimed dexamethasone dihydrogenphosphate disodium-containing gel preparations.

Third, Applicant has confirmed the stability data discussed in specification page 5, thereby rebutting any *prima facie* case of obviousness. As previously presented in the Preliminary Amendment filed September 18, 2003, Applicant submitted stability data for an ophthalmic gel preparation of dexamethasone dihydrogenphosphate disodium. (Additional information submitted with the Preliminary Amendment filed September 18, 2003, is included in Appendix XI.) Formulation 1 corresponds to the presently claimed invention. Formulation C1 is a similar formulation but the pH value was adjusted to 6.3 to 7.3. Formulation C1 exhibited an unacceptable decrease in the amount of dexamethasone dihydrogenphosphate

disodium. In contrast, Formulation 1 of the present invention exhibited only about 1% decomposition of dexamethasone dihydrogenphosphate after 18 months.

The relevant data from the attached sheets is reproduced below.

Formulation 1

Component	**Amount (g)**	**Weight %**
Carbopol 980	3.00	0.300
Dexamethasone-Na-Phosphate	1.107	0.1107
Cetrimide	0.100	0.0100
Na-edetate	0.100	0.0100
Sorbitol	49.00	4.900
NaOH	1.50	0.15
Water	945.193	94.5193
Total	1000.00	100%
pH Specification	7.6-8.0	

Formulation C1

Component	**Amount (g)**	**Weight %**
Carbopol 980	1.5	0.30
Dexamethasone-Na-Phosphate	0.4925	0.09850
Cetrimide	0.05	0.01
Na-edetate	0.05	0.01
Sorbitol	24.50	4.900
NaOH	0.60	0.12
Water	472.8075	94.5615
Total	500.0000	100%
pH Specification	6.3-7.3	

Formulation 1 **Storage Conditions**

	Months	21°C/45%	25°C/60%	30°C/70%
Content (%) of Dexamethasone	0	102.0		
	3	99.0	99.8	100.1
	6	99.6	101.6	101.1
	9	102.3	101.7	101.6
	12	99.7	98.3	97.6
	18	101.3	100.9	99.1
Decomposition (%) of Dexamethasone	0	0.2		
	3	0.2	0.2	0.2
	6	0.4	0.5	0.5
	9	0.5	0.5	0.6
	12	0.5	0.6	0.7
	18	0.7	0.7	0.8

Formulation C1 **Storage Conditions**

	Months	21°C/45%	26°C/60%	31°C/70%
Content (%) of Dexamethasone	0	96.2		
	3	95.7	96.2	94.5
	7	95.8	94.7	92.5
	12	95.1	91.7	89.2
	18	86.3	86.0	83.9
Decomposition (%) of Dexamethasone	0			
	3	1.4	1.6	1.8
	7	2.4	2.9	3.1
	12	3.6	3.5	4.0
	18	10.7	11.2	12.9

This stability data confirm, as disclosed in the present specification, that if gel formulations of dexamethasone dihydrogenphosphate disodium are prepared at a pH value above 7.3, the formulations will provide a storage stability required for pharmaceutical preparations.

C. Claim 8

For the same reasons stated in section VII.B., supra, the Section 103(a) rejection is improper as to dependent claim 8.

Additionally, it is submitted that the references especially do not suggest a dexamethasone dihydrogenphosphate disodium-containing gel formulation having a pH value between 7.6 and 8.2, as defined in claim 8. Also, to the extent the Examiner has criticized the stability data previously presented as not commensurate in scope with the claims, applicants note Formulation A of this stability data employs a pH value of 7.6 to 8.0.

In light of the foregoing arguments, applicants request that the outstanding rejection be reversed and that the pending claims 7-16 be allowed.

Respectfully submitted,

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Dated: September 22, 2006

VIII. Claims Appendix

The claims under appeal are as follows:

7. An ophthalmic gel preparation comprising:

dexamethasone dihydrogenphosphate disodium;

a gel forming, pharmaceutically acceptable substance in an amount effective for adjusting the viscosity of the preparation so that the preparation has the form of a gel; and

a pH regulating component in an amount effective to provide the preparation with a pH value above 7.3.

8. The preparation according to claim 7, wherein the preparation has a pH value between 7.6 and 8.2.

9. The preparation according to claim 8, wherein the preparation has a pH value between 7.8 and 8.0.

10. The preparation according to claim 7, wherein the gel-forming substance comprises a carbomer.

11. The preparation according to claim 10, wherein the gel-forming substance is a carbomer of the type Carbopol 980 NF.

12. The preparation according to claim 10, wherein the preparation comprises 0.05 to 1% by weight of the carbomer.

13. The preparation according to claim 12, wherein the preparation comprises 0.1 to 0.6% by weight of the carbomer.

14. The preparation according to claim 7, further comprising benzododecinium chloride.

15. The preparation according to claim 7, further comprising an isotonic agent and gelating agent.

16. The preparation according to claim 15, wherein the isotonic agent comprises sorbitol and the gelating agent comprises sodium edetate.

IX. Evidence Appendix

Attachments to Preliminary Amendment Filed September 18, 2003

Formulation 1

Discussed in Section VII.B

(2)

Dr. Mann Pharma - Berlin

Formulation B1

HERSTELLBERICHT FÜR ENTWICKLUNGSCHARGEN - Augengele -

Präparat:	Ch.-Bez.:	Ansatzgröße	Herstelldatum	TEIL
Dexamethason Gel	[redacted]	1Kg	[redacted]	I

Bemerkungen (z. B. Grund der Herstellung):

Hersteller: FD
Prüfer (Teil 1): DH/15
Prüfdatum: [redacted]

Lfd. Nr.	WE-Nr.	Bezeichnung	Einwaage (g)	Gehalt nach Analyse mg/g	der Deklaration (%)
1	0860036	Carbopol 980	3,00		
2	0450268	Dexamethason-21-dihydrogen~~sulfat~~ phosphat *	1.107		102.8
3	0560360	Cetrimid	0,100		99.7%
4	0160055	Na-edetat	0,100		
5	0760322	Sorbitol	49,00		
6	0760214	NaOH, fest	1,50		
7	/	dest. Wasser	↓		
		* H_2O-Gehalt der Substanz beachten = 11.05%	945,193		

Stability test: Dexamethason Gel Prod. n

Batch number: [redacted]
Batch size: 1 kg
Container: 5 g Polyfoil tubes
Place ofmanufacture: Dr. Mann Pharma, Berlin
Date of manufacture: [redacted]
Date of storage:

Formulation B 1
pH 7.6 – 8.0

Test date	months
10/96	0
02/97	3
05/97	6
08/97	9
11/97	12
05/98	18

Test for	Specification (release)	Months	Storage conditions		
			21 °C/45 %	25 °C/60 %	30 °C/70 %
Content [%] Dexamethasone sodium phosphate	95 - 105	0	102.0		
		3	99.0	99.8	100.1
		6	99.6	101.6	101.1
		9	102.3	101.7	101.6
		12	99.7	98.3	97.6
		18	101.3	100.9	99.1
Decomposition [%] Dexamethasone	n.m.t. 3	0	0.2		
		3	0.2	0.2	0.2
		6	0.4	0.5	0.5
		9	0.5	0.5	0.6
		12	0.5	0.6	0.7
		18	0.7	0.7	0.8
Content [%] Cetrimide	90 - 110	0	99.7		
		3	99.3	100.3	99.6
		6	98.3	99.0	99.0
		9	100.5	99.0	100.0
		12	100.2	99.2	99.4
		18	99.5	100.6	101.4
Transmission [%]	n.l.t. 85	0	88.4		
		3	89.6	89.7	87.0
		6	88.8	88.9	89.0
		9	86.6	89.3	89.2
		12	89.3	88.6	89.5
		18	87.0	86.9	87.5
pH value	7.6 - 8.0	0	7.7		
		3	8.0	7.9	7.9
		6	7.7	7.7	7.7
		9	7.7	7.7	7.6
		12	7.7	7.7	7.7
		18	7.8	7.8	7.7
Osmolality [mosmol/kg]	290 - 320	0	305		
		3	303	304	304
		6	304	305	306
		9	312	307	308
		12	308	307	307
		18	305	306	306
Viscosity [mPa·s]	2400 - 3400	0	3075		
		3	2802	3451	3308
		6	3502	3158	3403
		9	2877	3178	3209
		12	3022	3175	3132
		18	3691	3804	3428

Stability test: Dexamethason Gel Prod[illegible]

(4)

Batch number: [redacted]
Batch size: 1 kg
Container: 5 g Polyfoil tubes
Place ofmanufacture: Dr. Mann Pharma, Berlin
Date of manufacture: [redacted]
Date of storage: [redacted]

Test date	months
10/96	0
02/97	3
05/97	6
08/97	9
11/97	12
05/98	18

Test for	Specification (release)	Months	Storage conditions		
			21 °C/45 %	25 °C/60 %	30 °C/70 %
Colour	B 9	0	B 9		
		3	B 9	B 9	B 9
		6	B 9	B 9	B 9
		9	B 9	B 9	B 9
		12	B 9	B 9	B 9
		18	B 9	B 9	B 9
Clearity and degree of opalecencef	n.m.t.standard of opalescence IV	0	n.m.t. IV		
		3	n.m.t. IV	n.m.t. IV	n.m.t. IV
		6	n.m.t. IV	n.m.t. IV	n.m.t. IV
		9	n.m.t. IV	n.m.t. IV	n.m.t. IV
		12	n.m.t. IV	n.m.t. IV	n.m.t. IV
		18	n.m.t. IV	n.m.t. IV	n.m.t. IV
Sterility	sterile	0	sterile		

Formulation C1

Discussed in Section VII.B

Dr. Mann Pharma - Berlin

C1 Formulation A

HERSTELLBERICHT FÜR ENTWICKLUNGSCHARGEN - Augengele -

Präparat:	Ch.-Bez.:	Ansatzgröße	Herstelldatum	TEIL
Dexamethason-Gel	GUG [redacted]	500 g	[redacted]	I

Bemerkungen (z.B. Grund der Herstellung):

Hersteller: [redacted]
Prüfer (Teil 1): [redacted]

Lfd.Nr.	WE-Nr.	Bezeichnung	Einwaage (g)	Gehalt nach Analyse (mg/g)	der Deklaration (%)
1	607 1021 5612	Carbopol 980	1.5		
2	1130227	Dexamethason-Na-phosphat	0.4925		96.17
3	1190210	Cetrimid	0.05		95.90
4	1020230	Edetinsäure, Dinatrium	0.05		
5	0830086	Sorbitol	24.50		
6	0330339	NaOH, fest	0.60		
7	/	Wasser für Injektionszwecke	472.8015		

HERSTELLUNG:

BESONDERHEITEN BEI DER HERSTELLUNG: Bei der Einwaage von Dexamethason-Na-phosphat wurde das Saccharose-Gehalt von 1.65 % nicht berücksichtigt.

Stabilitäts[redacted]fung von : Dexamann visc. Prä[redacted]. 190

Chargennummer [redacted]

(10)

Chargengröße : 500 g
Behältnis : 5 g-Polyfoil-Kanülentube, Innenbeschichtung: HDPE
Herstellungsort : Dr. Mann Pharma, Berlin
Herstelldatum [redacted]
Erstuntersuchung
Einlagerungsdatum
Prüfdatum : Monate

Formulation ACI
pH 6.3 - 7.3

05/94	3
09/94	7
02/95	12
08/95	18

Prüfung auf	Spezifikation	Lagerzeit in Mon.	Lagerungsbedingungen			
			5°C	21°C/45%	26°C/60%	31°C/70%
Gehalt in % Dexamethason-dihydogen-phosphat	90 - 105	0		96,2		
		3	96,8	95,7	96,2	94,5
		7	-	95,8	94,7	92,5
		12	-	95,1	91,7	89,2
		18	-	86,3	86,0	83,9
Gehalt in % Cetrimid	90 - 105	0		95,9		
		3	-	-	-	-
		7	-	101,3	101,6	99,0
		12	-	98,0	97,7	97,4
		18	-	100,2	99,3	99,3
Dexamethason in %	max 10 %	0		n.n.		
		3	0,7	1,4	1,6	1,8
		7	-	2,4	2,9	3,1
		12	-	3,6	3,5	4,0
		18	-	10,7	11,2	12,9
Transmission in % (bei 425 nm)	> 85 %	0		91,8		
		3	95,2	95,3	94,6	95,4
		7	-	-	-	-
		12	-	93,1	93,6	-
		18	-	94,9	94,3	93,9
pH-Wert	6,3 - 7,3	0		7,2		
		3	7,0	7,0	7,0	7,0
		7	-	7,0	7,0	7,0
		12	-	6,9	6,9	7,0
		18	-	7,1	7,0	7,0
Osmolalität (mosm/kg)	285 - 335	0		304		
		3	304	300	298	301
		7	-	301	300	303
		12	-	328	299	303
Leitfähigkeit (µS/cm)	7 - 12	0		8,7		
		3	9,9	10,1	10,2	10,0
		7	-	-	-	-
Brechungsindex (n_D)	1,339 - 1,341	0		1,3408		
		3	1,3407	1,3406	1,3405	1,3404
		7	-	1,3407	1,3406	1,3406
Viskosität (mPa·s)	2000 - 3000	0		2844		
		3	2622	2642	2652	2734
		7	-	2550	2799	2724
		12	-	2911	2875	-
		18	-	2918	2857	-
Aussehen	klar (DAB 10/ Ph. Eur.)	0		klar		
		3	klar	klar	klar	klar
		7	-	klar	klar	klar
		12	-	klar	klar	klar
		18	-	klar	klar	klar
Farbe	B 9 (DAB 10/ Ph. Eur.)	0		B 9		
		3	B 9	B 9	B 9	B 9
		7	-	B 9	B 9	B 9
		12	-	B 9	B 9	B 9
		18	-	B 9	B 9	B 9
Mikrobiolog. Qualität	steril	0		steril		

n.n. = nicht nachweisbar
- = nicht untersucht

[redacted]

X. Related Proceedings Appendix

(None)